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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
CINCINNATI, OHIO 45268

December 2, 1992

SUBJECT: Provisional Non-cancer and Cancer Toxicity Values for Potassium Perchlorate (CASRN 7778-74-7) (Aerojet General Corp./CA)

FROM: Joan S. Dollarhide
Associate Director
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Chemical Mixtures Assessment Branch

TO: Dan Stralka
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Region IX

As per your request dated October 9, 1992, we have evaluated the toxicity and potential carcinogenicity of potassium perchlorate, and attempted to derive toxicity values. We derived a provisional RfD of 1E-4 mg/kg-day for potassium perchlorate for effects on the thyroid-pituitary axis. The NOAEL was obtained from an acute study in which potassium perchlorate caused release of iodine from the thyroid gland. This was considered the first step in a cascade of effects which includes decrease in plasma levels of T_3 (triiodothyronine) and T_4 (tetraiodothyronine or thyroxin), increase in TSH (thyroid stimulating hormone) production, and increase in size and weight of the thyroid. The use of an acute study for deriving the RfD is plausible because the effects seen in the acute study appear to be by the same mechanism as the effects seen in chronic studies. However, since data concerning long-term, low-dose exposure are limited, confidence in the provisional RfD is low.

No quantitative risk estimate for carcinogenicity was derived for perchlorate compounds because of the limitations of the data. However, because thyroid tumors were observed in both mice and rats following long-term administration of sodium or potassium perchlorate, a weight-of-evidence classification of B2, probable human carcinogen, is appropriate. The combined use of data for the sodium and potassium salts for the classification is appropriate because their actions on the thyroid are similar. The use of this classification is limited to these two salts since there are no relevant data on other perchlorate compounds.

Attached please find Risk Assessment Issue Paper for:

- Provisional Non-cancer and Cancer Toxicity Values for Potassium Perchlorate (CASRN 7778-74-7)

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Please do not hesitate to contact the Superfund Technical Support Center at (513) 569-7300 if you have additional questions.

Attachment

cc: J. Dinan (OS-230)
B. Means (OS-230)
C. Sonich-Mullin

Attachment

Risk Assessment Issue Paper for:
Provisional Non-cancer and Cancer Toxicity Values for
Potassium Perchlorate

I. INTRODUCTION

RfDs or cancer risk assessments for perchlorate-containing compounds, including potassium perchlorate (CASRN 7778-74-7), ammonium perchlorate (CASRN 7790-98-9), lithium perchlorate (CASRN 7791-03-9), sodium perchlorate (CASRN 7601-89-0) and perchloric acid (CASRN 7601-90-3) are not discussed on IRIS (U.S. EPA, 1992a) or the HEAST (U.S. EPA, 1992b). The RfD/RfC and CRAVE status reports (U.S. EPA, 1992c) contain no reference to Work Group activity for RfDs or cancer risk assessments on any of the perchlorate-containing compounds. The Office of Drinking Water lists no drinking water regulations or health advisories for perchlorate-containing compounds (U.S. EPA, 1992d). There are no documents for any perchlorate-containing compounds on the CARA list (U.S. EPA, 1991).

To identify research reports pertinent to the derivation of provisional non-cancer and cancer toxicity values for perchlorates, computer searches of the following databases were conducted for potassium perchlorate, ammonium perchlorate, lithium perchlorate, perchloric acid and sodium perchlorate: MEDLINE, 1965-1992; TOXLINE, 1965-1992; CANCERLIT, 1965-1992; TSCATS; RTECS; and HSDB. In addition, references cited in the ICF Technology, Inc. report "On the Toxicity of Perchlorates" (Undated) were retrieved and examined.

II. DERIVATION OF AN RfD FOR POTASSIUM PERCHLORATE

A. HUMAN TOXICITY DATA

A single epidemiological study of humans occupationally exposed to perchloric acid or its salts was identified, but the lack of quantification of exposure conditions and the high probability that workers were exposed to many chemicals other than perchlorate precludes the use of the data in risk assessment for potassium perchlorate. Rockette and Arena (1983) conducted a death certificate-based historical prospective study of workers in a U.S. chemical plant in which magnesium perchlorate and perchloric acid were used in one work area along with many other chemicals. The authors concluded that "... a high cause-specific mortality rate for a particular time period and work area could not be interpreted as being due to a specific chemical since an employee was exposed to many other chemicals...".

Repeated oral administration of potassium perchlorate (and in a few cases sodium perchlorate) has been used to control Graves' Disease in humans. Symptoms of this disease include increased synthesis and secretion of iodide-containing hormones into the blood by the thyroid gland ("thyroid hormones" include triiodothyronine [T3] and tetraiodothyronine [T4 or thyroxin]), thyroid gland enlargement, increased basal metabolism and loss of weight. Perchlorate inhibits the excessive synthesis and secretion of thyroid hormones (and can thus relieve the symptoms of Graves' Disease) by competitively inhibiting the accumulation of iodide in the thyroid (see review of evidence in the next paragraph). In normal individuals, the synthesis and secretion of thyroid hormones are controlled, not only by iodide levels in the thyroid, but also by a feedback mechanism involving the production of thyroid stimulating hormone (TSH) by the anterior pituitary (see U.S. EPA, 1988 for a review with further details). TSH causes the thyroid to initiate new thyroid hormone synthesis; its production in the pituitary gland, in turn, responds to blood levels of T3 and T4. When circulating levels of T3 and T4 decrease, the production of TSH in the pituitary increases; conversely, increased levels of circulating T3 and T4 lead to decreased pituitary production of TSH.

Stanbury and Wyngaarden (1952) reported that the uptake of tracer levels of I^{131} into the thyroid glands of 3 patients with Graves' disease was markedly inhibited for as long as 6 hours when 100 mg of potassium perchlorate was given orally 1 hour prior to administration of the tracer. Administration of 100 mg potassium perchlorate resulted in the nearly complete release, within 30 minutes, of previously accumulated I^{131} from the thyroids of Graves' disease patients previously treated with tracer amounts of I^{131} and 1-methyl-2-mercaptoimidazole (an antithyroid agent that inhibits the incorporation of iodide into thyroid hormone molecules); with smaller doses of potassium perchlorate (e.g. 3, 10 or 50 mg) the discharge of I^{131} was incomplete (Stanbury and Wyngaarden, 1952). Eight patients were included in these I^{131} release studies.

Based on the Stanbury and Wyngaarden (1952) results with Graves' Disease patients and similar results with normal rats (Wyngaarden et al., 1952, 1953), physicians began treating Graves' disease patients with orally administered potassium perchlorate. Subsequent <u>in vitro</u> studies of iodide transport in sheep thyroid tissue slices (Wolff and Maurey, 1962) and phospholipid vesicles (Saito et al., 1983) have confirmed that perchlorate competitively inhibits iodide transport. Perchlorate has been shown to produce effects on thyroid function in healthy humans that are similar to those seen in patients with hyperthyroidism. Oral administration, three times daily for eight days, of 200-mg doses of potassium perchlorate significantly enhanced the secretion of non-thyroxine iodine from

the thyroid in 5 healthy human volunteers (Burgi et al., 1974). In addition, the authors concluded that their data and those from a previous study (DeGroot and Buhler, 1971) suggested that iodide uptake by the thyroid was completely blocked by this dosage of perchlorate.

Daily repeated doses of 400-800 mg (usually 200 mg given at intervals, 2-4 times a day) were used effectively to inhibit overactive thyroid in the first years of this practice (Godley and Stanbury, 1954). Later, initial daily doses as high as 1600-2000 mg/day were administered, sometimes followed by maintenance daily doses of 200-800 mg/day (Anonymous, 1969; Everd, 1976; Crooks and Wayne, 1960).

The use of repeatedly administered potassium perchlorate to inhibit excessive thyroid activity (i.e., excessive synthesis and secretion of thyroid hormones) has been associated with infrequently occurring side effects, including skin rashes, sore throat, gastrointestinal irritation and hematological effects (agranulocytosis). Early studies found the side effects to be reversible upon cessation of perchlorate administration, but more widespread use of perchlorate revealed several cases of severe hematological side effects.

Godley and Stanbury (1954) observed no "serious" complications in 24 patients treated with 200 mg potassium perchlorate four times daily (800 mg/day), but mentioned that gastrointestinal irritation occurred in 2 patients.

Crooks and Wayne (1960) observed 1 case of skin rash and 3 cases of nausea among 35 patients treated with 600 mg/day and 165 patients given 1000 mg/day; in another group of 10 patients given 1500 mg/day and 40 patients given 2000 mg/day, 5 cases of skin rash, 2 cases of nausea and 1 case of agranulocytosis occurred. Leucocyte counts returned to normal in the patient with agranulocytosis when potassium chlorate administration (1500 mg/day) was stopped. The authors did not specify the durations of treatment experienced by the patients in this study, but reported that the mean time for thyrotoxic symptoms to subside was 9.4 weeks among patients treated with 1000 mg potassium perchlorate/day.

Morgans and Trotter (1960) reported that 3% of 180 patients treated with 400 to 1000 mg/day and 18% of 67 patients (12/67) treated with 1200-2000 mg/day doses of potassium perchlorate showed toxic reactions including skin rash, sore throat and gastrointestinal irritation within 2-3 weeks of the commencement of treatment. The 12 reactions displayed by patients receiving the higher dosage levels consisted of 2 cases of rash with fever, 8 cases of rash alone and 2 cases of lymphadenopathy.

Between 1961 and 1966, several cases of fatal aplastic anemia were reported in female patients receiving long-term potassium perchlorate treatment for hyperthyroidism. Reported cases include a woman receiving 600 to 800 mg/day for 33 weeks (Hobson, 1961), a woman treated for 3 months with 600-1000 mg/day for 3-4 months, (Johnson and Moore, 1961), a woman treated with 400-600 mg/day for 6 months (Fawcett and Clark, 1961), a woman treated with 450-800 mg/day for 6 months (Krevans et al., 1962), a woman receiving 400 to 600 mg/day for 4-5 months (Gjemdal, 1963), and a woman receiving 1000 mg/day for 2 months (Barzilai and Sheinfeld, 1966). Barzilai and Sheinfeld (1966) also reported a fatal case of agranulocytosis in a woman treated with 1000 mg/day potassium perchlorate for a "few" months. Other case reports are available concerning non-fatal agranulocytosis in patients treated with 1000 mg/day for 12 days (Southwell and Randall, 1960) or 4 months (Sunar, 1963). The occurrence of these hematological side effects, although infrequent, led to a decreased use of potassium perchlorate in the control of hyperthyroidism (Everd, 1976; Connell, 1981). Similar infrequently occurring hematological effects have been reported with the repeated administration of another class of antithyroid agents, thioamides, including propylthiouracil and carbimazole (Anonymous, 1969; Everd, 1976; Biswas et al., 1991). The thioamide drugs block the biosynthesis of thyroid hormones without interfering with iodide transport.

Fatal acute liver atrophy occurred in a patient who received 600 mg/day sodium perchlorate for 13 months (Kotzaurek, 1965). A nephrotic syndrome was observed in a patient treated with sodium perchlorate (a total of 118 g was administered over a period of 5 months) (Weber and Wolf, 1969). Other corroborative reports supporting the existence of a possible association between liver or kidney disease and repeated perchlorate administration were not located.

B. ANIMAL TOXICITY DATA

RTECS (NIOSH, 1992) lists several acute toxicity values for orally administered perchlorates taken from the Russian literature, including LD50 values of 1100 mg/kg for rats and 400 mg/kg for dogs given perchloric acid; a rat LD50 of 2100 mg/kg for sodium perchlorate; and LD50 values for ammonium perchlorate of 4200 mg/kg for rats, 1900 mg/kg for mice, 1900 mg/kg for rabbits and 3310 mg/kg for guinea pigs.

In a study of anions that interfere with the accumulation and retention of iodide in the thyroid gland of the rat, Wyngaarden et al. (1952) provided 0 (tap water controls) or 1% potassium perchlorate in drinking water to groups of 3 male Wistar rats provided a "regular" diet for 17 days. From water intake data, the authors calculated the average intake of

potassium perchlorate to be 233.5 mg/100 g body weight/day (2335 mg/kg-day). Weights and iodine contents (both trichloroacetic acid-soluble and -precipitable iodine) of thyroids were determined, and thyroids were examined histologically. Body weights were similar between control and perchlorate-treated rats throughout the treatment period. Compared with controls, perchlorate-treated rats displayed enlarged thyroids (average weight of 31.9 mg compared with 11.4 mg for controls), marked hyperplasia of the thyroid, and decreased thyroid iodine concentrations (average contents, in μg/mg tissue, were 0.018 for soluble iodine compared with 0.099 for controls, and 0.021 for trichloroacetic acid-precipitable iodine compared with 0.700 for controls). Another group of three rats was treated for the same period of time with tap water and a diet containing 0.1% propylthiouracil (0.55 mg/kg-day, calculated by the authors from food intake), an antithyroid agent that is thought to interfere with the incorporation of iodide into thyroid hormones, but not with iodide transport. Propylthiouracil-treated rats displayed thyroid effects similar to those seen in perchlorate-treated rats (increased thyroid weight, hyperplasia of the thyroid and decreased thyroid iodine content), but, in contrast to perchlorate-treated rats, propylthiouracil-treated rats also displayed decreased body weights throughout the treatment period (> 10% decrease).

Kessler and Kruskemper (1966) provided potassium perchlorate in drinking water at a concentration of 0 or 1% to male Wistar rats (120-150 days old at the beginning of treatment) for up to 2 years. Body weights and thyroid weights were reported for groups of 6-8 rats sacrificed after 0, 40, 120, 220 and 730 days of treatment. Thyroid glands from the animals were examined histologically. Using body weight data provided in the report to calculate a time-weighted average body weight of 0.336 kg and a water consumption rate of 0.045 L/day calculated with the allometric equation recommended by U.S. EPA (1987), a dose of 1339 mg/kg-day is estimated. Body weights of control and treated animals were comparable throughout the experiment. In contrast, thyroid weights (both absolute or relative to body weight) were markedly increased in treated rats compared with controls at each examination interval. Histological examination of thyroids from treated rats at 40 days revealed follicular cell hyperplasia (i.e., small follicles with high epithelia and large nuclei, numerous mitoses, colloid resorption and low-grade mesenchymal reaction). The authors characterized these changes as typical for a thyroid gland stimulated by TSH for a relatively short period of time. After 200 days of perchlorate treatment, diffusely degenerative changes with fibrosis and increased colloid were observed. The authors commented that the course of the histological changes in the thyroid was similar to that produced by long-term administration of thiouracil, another antithyroid agent. The authors further reported that four of eleven rats treated with potassium perchlorate for 2 years

displayed benign tumors of the thyroid gland and that 20 untreated Wistar control rats displayed no thyroid gland tumors.

Gauss (1972) provided female NMRI mice ad libitum access to a diet containing 0 or 1% potassium perchlorate for up to 160 days. Mice were between 50 and 60 days old at the beginning of treatment and weighed between 19 and 28 grams (average = 23.23 g). An 11.6 percent decrease in body weight was observed in the treated mice during the first two months of treatment; body weight data for longer treatment periods were not reported. Assuming a body weight of 23 g (the approximate value for treated mice after 2 months; estimated from the report's graph of a regression of body weight and treatment days) and a food consumption value of 4.625 g/day (U.S. EPA, 1987), a dose of 2011 mg/kg-day is estimated. Thyroid glands were examined histologically at 10-20 day intervals through 160 days. Thyroid volume, nuclei volume and height of epithelial follicles were increased in treated mice throughout the treatment period compared with control values. The English translation summary of the histological examinations described a progressive change in the histological appearance of the thyroid of treated mice, beginning with colloid loss, nuclei volume expansion and rising epithelium height, followed by the appearance of hyperplasia and hypertrophy of the thyroid parenchyma. At later stages of the treatment period, hyperplastic follicles, areas of adenomatic tissue, adenoma complexes and secreting cystadenomas were observed; however, no progression to malignancy was apparent. Incidences for the number of animals with tumors were not provided in the tables, figures or English summary of the report; however, an English translation of the report's text was not available for this review.

Mannisto et al. (1979) measured serum levels of TSH, T3 and T4 by radioimmunoassays in groups of 5-6 male Sprague-Dawley rats weighing 180-220 grams that were provided potassium perchlorate in drinking water at concentrations of 0, 10, 50, 100 or 500 mg/L for 4 days or propylthiouracil at concentrations of 0, 1, 5, 10, 25 or 50 mg/L for the same period. Potassium perchlorate doses of 0, 1.5, 7.6, 15.3, and 76.3 mg/kg-day are calculated assuming a body weight of 0.2 kg and a water consumption rate of 0.0305 L/day (U.S. EPA, 1987). Both compounds produced statistically significant increases in serum TSH levels and decreases in serum T3 and T4 levels. Significant changes in all three parameters were measured in rats treated with concentrations $\geq$ 10 mg/L propylthiouracil or $\geq$ 100 mg/L potassium perchlorate. At 50 mg/L potassium perchlorate, significantly decreased levels of T3 and T4 were measured, but the increase in TSH was not statistically significant. At 10 mg/L potassium perchlorate, the levels of TSH, T3 and T4 were essentially unchanged from control values.

Hiasa et al. (1987) measured serum levels of T3, T4 and TSH by radioimmunoassay in groups of 20 male Wistar rats following

administration of 0 or 1000 ppm potassium perchlorate in the diet for 20 weeks. Separate groups of 20 rats received single injections of 28 mg/kg of N-bis(2-hydroxypropyl)nitrosamine (DHPN, a demonstrated initiator of thyroid tumors promoted by propylthiouracil) followed by 20 weeks administration of 0 or 1000 ppm potassium perchlorate in the diet. Assuming a body weight of 0.34 kg (the average final body weight of rats treated with perchlorate alone) and a food consumption value of 27.4 g/day (U.S. EPA, 1987), an estimated dose of 80.7 mg/kg-day is calculated. Thyroid weights (both absolute and relative) were significantly increased, compared with controls, in perchlorate-treated rats with or without DHPN treatment, but no effects on body or liver weights were seen. Serum levels of TSH were significantly increased in perchlorate-treated rats (with or without DHPN injection) compared with control values. Serum levels of T4 were decreased in perchlorate-treated rats, but the decrease was statistically significant only in the DHPN-perchlorate rats. Levels of T3 were comparable in perchlorate rats (with or without DHPN) and control rats. DHPN treatment alone produced no effects on body weight, thyroid weight, liver weight or serum levels of TSH, T3 or T4. Thyroid tumors developed in 20/20 DHPN-perchlorate rats and in 1/20 DHPN rats. No thyroid tumors were observed in control rats or in rats treated only with perchlorate. Follicular hyperplasia of the thyroid was found in 1 of the 20 rats treated with perchlorate alone; diffused small follicles were also observed in the thyroids of these rats, but the report did not specify the extent or incidence of these "non-tumorous" lesions.

Pajer and Kalisnik (1991) provided groups of 36 female BALB/c mice, 6 weeks of age, 0 (tap water) or 1.2% sodium perchlorate in drinking water for up to 46 weeks. Eight or 12 weeks after the beginning of the experiment, 12 perchlorate mice and 12 control mice were totally irradiated with 0.8 Gy on 5 consecutive days, at a dose rate of 1.45 Gy/minute of gamma rays, so that each mouse received a total of 4 Gy. A dose of 2147 mg sodium perchlorate/kg-day was calculated using a reference body weight of 0.0353 kg and water consumption rate of 0.0063 L/day (U.S. EPA, 1987). Thirty animals died during the experimental period; further details concerning these early deaths were not provided by the authors. Forty-two animals were sacrificed at 46 weeks for histological examination of the thyroid glands and pituitaries. Obvious treatment-related histological changes were observed in the thyroid and pituitary, including thyroid follicular cell carcinoma. Immunoperoxidase staining of pituitary thyrotropic cells with antihuman TSH serum provided qualitative evidence of increased TSH production in the pituitary. The incidences of thyroid follicular cell carcinoma were 0/22 in control groups (included were nonirradiated and irradiated controls), 5/6 in perchlorate-nonirradiated mice and 14/14 in perchlorate-irradiated mice. No medullary carcinoma was found. Perchlorate treatment was associated with increased total

volumes of the thyroid gland and the distal parts of the anterior pituitary (adenohypophysis), as well as increased average volumes and increased numbers of epithelial, thyrotropic and parafollicular cells.

Brown-Grant (1966) provided 1% potassium perchlorate or 1% potassium chloride in drinking water to pregnant Wistar rats from gestation day 2 to day 8. Average doses were reported to be 237 mg $KClO_4$/rat/day and 371 mg KCl/kg-day (741 mg $KClO_4$/kg-day and 1159 mg KCl/kg-day, assuming a body weight of 0.32 kg; U.S. EPA, 1987). Birth of a live litter occurred in 7/11 KCl dams and 8/11 $KClO_4$ dams. Examination of fetuses for developmental defects was not conducted. The four KCL-control dams and three $KClO_4$-dams that did not give birth displayed no visible signs of implantation in their uteri. The author concluded that 1% potassium perchlorate in drinking water had no effect on the course of pregnancy in rats.

Brown-Grant and Sherwood (1971) provided 1% potassium perchlorate or 0.1% potassium iodide in drinking water to pregnant Wistar rats that were also lactating. Administration began on day 0 of pregnancy and continued until day 12 or 13. Non-lactating pregnant Wistar rats were provided with 0.1% KCl or 0.1% KI by a similar protocol. Untreated controls were not included in the experiment. The suckling litters were removed on days 9 or 10, and all dams were killed on day 12 or 13 and examined for the number of implantation sites. The incidences of dams with implantation sites were 9/9 for 0.1% KCl-nonlactating dams, 8/8 for 0.1% KI-nonlactating dams, 9/9 for 0.1% KI-lactating dams and 7/10 for 1% $KClO_4$-lactating dams. The number of implantation sites per dam with sites was comparable among the groups: 11 for 1% $KClO_4$-lactating, 0.1% KI-lactating and 0.1% KI-nonlactating dams, and 12 for 0.1% KCl-nonlactating dams. Relative thyroid weights in dams appeared to be increased in dams treated with 1% $KClO_4$ compared with values for 0.1% KI-lactating, 0.1% KI-nonlactating and 0.1% KCl-nonlactating dams (7.3$\pm$ 0.3 mg/100 g body weight versus 6.2$\pm$0.2, 6.5$\pm$0.3 and 5.6$\pm$0.3, respectively). Thyroid weights of 1% $KClO_4$ offspring were elevated compared with 0.1% KI offspring (21.1$\pm$1.0 mg/100 g versus 14.6$\pm$0.6); thyroid weights for offspring from nonlactating dams were not measured. The authors concluded that the treatment with potassium perchlorate had no "significant" effect on blastocyst survival or the ability to implant under conditions delaying implantation (i.e., concurrent lactation).

Postel (1957) reported that provision of 1% potassium perchlorate in drinking water to pregnant guinea pigs during gestation days 21 through 48 produced enlarged thyroids in the fetuses (mean weight of 491$\pm$157 mg/100 g body weight) compared with thyroids of control fetuses (32.3$\pm$3.4 mg/100 g body weight). In contrast, the 37-day treatment with perchlorate did not

produce enlarged thyroids in the dams. Enlarged fetal thyroids also occurred when perchlorate treatment was accompanied by daily subcutaneous administration of T3 at doses as high as 32 μg/dam/day. From water intake and body weight data, the authors calculated an average daily dose to the dams of 740 mg potassium perchlorate/kg-day. The fetuses were not examined for other developmental effects. In a separate experiment, 0 or 1% potassium perchlorate was administered to nonpregnant female guinea pigs for 30, 60 or 90 days. Thyroid enlargement and intense hyperplasia, compared to controls, were not apparent in exposed adults at 30 days, but were readily apparent after 60 or 90 days of treatment.

C. PHARMACOKINETIC DATA

Durand (1938) measured rapid urinary elimination of perchlorate in two human subjects who ingested 0.784 g sodium perchlorate in 100 g of water. Fifty per cent of the doses were eliminated in the urine 5 hours after administration; by 48 hours after administration, urinary elimination accounted for 95% of the dose. These results indicate that perchlorate is rapidly and completely absorbed from the gastrointestinal tract and rapidly eliminated from the body.

Goldman and Stanbury (1973) examined the pharmacokinetic behavior of intraperitoneal injections of ^{36}Cl-labeled potassium perchlorate (0.1-0.2 uCi with a specific activity of 240 uCi/mmole) in male Sprague-Dawley rats weighing 0.20-0.35 kg and previously maintained on a low-iodine diet. Groups of animals were killed at 2, 8, 24 and 96 hours after administration. Low levels of radiolabel were found in the thyroid; peak concentrations of about 3.2% of dose per g thyroid were measured at about 4 hours. At 96 hours, the retention of label in the thyroid was higher than retention in the kidney, spleen, liver or brain, but was less than 4% of the maximal levels measured at 4 hours. Most of the administered radiolabeled perchlorate was excreted in the urine. The excretion proceeded exponentially with a half-life of approximately 20 hours. The authors reported that this rate was similar to excretion rates for ^{131}I in rats measured by other investigators.

D. DERIVATION OF AN RfD

The human and animal data reviewed in the previous sections demonstrate that perchlorate can inhibit the production of iodide-containing thyroid hormones by competitively inhibiting iodide accumulation in the thyroid. The short-term consequence of this action is a response by the pituitary gland to produce TSH which in turn stimulates diffuse cell division and growth of the thyroid gland. With long-term TSH stimulation, diffuse

thyroid hyperplasia may progress to nodular proliferation of follicular cells and eventually to neoplasia (U.S. EPA, 1988). This sequence of events has been observed to varying degrees in several studies with rats or mice orally exposed to the high doses of perchlorate salts in the following list: 2335 mg $KClO_4$/kg-day for 17 days (Wyngaarden et al., 1952); 1339 mg $KClO_4$/kg-day for 2 years (Kessler and Kruskemper, 1966); 2011 mg $KClO_4$/kg-day for 160 days (Gauss, 1972); and 2147 mg $NaClO_4$/kg-day for 46 weeks (Pajer and Kalisnik, 1991). The disturbance of the function of the thyroid-pituitary axis appears to be the critical effect from exposure to perchlorate salts; other effects with long-term exposure have not been described except for infrequently occurring frank hematological effects described in humans therapeutically treated with perchlorate (see discussion in following paragraphs). The progressive effects on the thyroid-pituitary axis observed in these animal studies are similar to those produced by iodine deficiency and other antithyroid agents such as propylthiouracil (see U.S. EPA, 1988). The available subchronic and chronic animal studies with perchlorate salts do not adequately describe thresholds for adverse effects on the thyroid-pituitary axis.

In shorter-term experiments with Sprague-Dawley rats given potassium perchlorate in drinking water for 4 days, however, Mannisto et al. (1979) described a dose-response threshold for the influence of potassium perchlorate on the function of the thyroid-pituitary axis. At drinking water concentrations of 10 mg/L (1.5 mg/kg-day) serum levels of TSH, T3 and T4 were unaffected compared with controls, thereby describing a NOEL for potassium perchlorate-induced functional disturbance of the thyroid-pituitary axis. The lowest adverse effect level in this study was the concentration of 50 mg/L (7.6 mg/kg-day) which produced statistically significant decreased levels of T3 and T4 and statistically nonsignificant increases in TSH levels. Hiasa et al. (1987) observed increased thyroid weights, increased serum TSH levels and decreased serum T4 levels in Wistar rats treated with 1000 ppm in the diet for 20 weeks (80.7 mg/kg-day), but did not include lower dietary concentrations in their study.

Clinical experience with repeated oral administration of potassium perchlorate to patients with hyperthyroidism showed that 200-mg doses administered 2-4 times a day (400-800 mg/day or 5.7-11.4 mg/kg-day, assuming a 70-kg body weight) were effective at inhibiting the excessive production of thyroid hormones and controlling other consequential signs of hyperthyroidism such as increased basal metabolism and body weight decrease (Godley and Stanbury, 1954; Crooks and Wayne, 1960; Anonymous, 1969; Everd, 1976). While perchlorate produces a beneficial effect for humans with overactive thyroids, it is expected that repeated administration of similar doses to normal or hypothyroidic humans would adversely disturb the function of the thyroid-pituitary

axis. Supporting evidence for this expectation includes the observation that oral administration of 200-mg doses of potassium perchlorate, three times per day, enhanced the secretion of non-thyroxine iodine from the thyroid and blocked iodide uptake in the thyroid in healthy humans (Burgi et al., 1974). For the purposes of RfD derivation, the dose of 5.7 mg/kg-day, the lower end of the range of clinically administered doses of potassium perchlorate, is designated a FEL, because the occurrence of frank side effects on the hematological system (agranulocytosis and aplastic anemia) in some hyperthyroidic patients receiving 5.7-11.4 mg/kg-day suggests that such effects also could occur infrequently in normal humans. Because it is inappropriate to derive an RfD from a FEL, the clinical data do not provide a suitable basis for RfD derivation. However, the data indicate that the threshold for perchlorate's effects on the thyroid-pituitary and hematological systems is below 5.7 mg/kg-day.

The early experiments by Stanbury and Wyngaarden (1952), however, examined the influence of acute doses of potassium perchlorate at lower dosage levels which may provide a suitable basis for RfD derivation. In these experiments, single 100-mg doses of potassium perchlorate (1.4 mg/kg, assuming a 70-kg body weight) prevented the accumulation of subsequently administered radiolabeled iodide in the thyroid of hyperthyroidic humans for 6 hours. When tracer administration and treatment with 1-methyl-2-mercaptoimidazole (to inhibit incorporation of iodide into T3 or T4) preceded perchlorate administration, 100 mg potassium perchlorate caused a nearly complete release of the tracer from the thyroid; single doses of 10 mg potassium perchlorate (0.14 mg/kg) also produced a release of radiolabeled iodide under similar conditions, but the release was not complete. Thus 1.4 mg/kg appears to be a LOAEL and 0.14 mg/kg a NOAEL for acute disturbance of iodide accumulation in the thyroid. It is assumed for the purposes of RfD derivation that repeated exposure to 1.4 mg/kg-day would lead to a functional disturbance of the thyroid-pituitary axis, including decreased synthesis of thyroid hormones and increased production of TSH, through an inhibition of iodide accumulation in the thyroid and that 0.14 mg/kg would insufficiently impair iodide accumulation to disturb the function of the thyroid-pituitary axis.

In the absence of human data for repeated exposure to perchlorate doses lower than those used clinically to alter function of the thyroid-pituitary axis, the acute human NOAEL of 0.14 mg/kg-day potassium perchlorate for functional disturbance of the thyroid-pituitary axis is recommended to serve as the basis for a chronic RfD for potassium perchlorate. The use of human data, albeit acute, for chronic RfD derivation appears preferable to the use of rat data (e.g., data from the studies of Mannisto et al., 1979 or Hiasa et al., 1987), because of the limited evidence that rats may be considerably less sensitive to perchlorate than humans. No effects on serum TSH, T3 or T4

levels were observed in short-term experiments with rats treated with 1.5 mg/kg-day potassium perchlorate for 4 days (Mannisto et al., 1979), but acute doses of 1.4 mg/kg potassium perchlorate effectively inhibited thyroidal iodide accumulation in humans for as long as six hours, thereby providing support for the speculation that continued exposure to such doses would inhibit the incorporation of iodide into T3 and T4, and consequentially lead to increased serum TSH levels and decreased T3 and T4 levels.

An uncertainty factor of 1000 is proposed for RfD derivation: 10 for the use of a less than chronic study, 10 for the protection of sensitive individuals (e.g., individuals with low-iodine diets and individuals with genetically impaired iodide accumulation systems in the thyroid) and 10 to account for database deficiencies including limited data for subchronic and chronic administration of low doses of perchlorate, the lack of developmental and 2-generation reproduction studies and limited data concerning the possible influence of perchlorate on the hematological system. Applying the uncertainty factor of 1000 to the acute human NOAEL of 0.14 mg/kg-day obtains a provisional RfD of 1.4E-4 mg/kg-day (rounded to 1E-4 mg/kg-day) for potassium perchlorate.

Confidence in the principal study is low because it examined only an acute manifestation (inhibition of iodide accumulation in the thyroid) of the proposed critical effect of long-term exposure to potassium perchlorate (functional disturbance of the thyroid-pituitary axis) in a few human patients with hyperthyroidism. Confidence in the data base is low to medium. The effect of chronic exposure to relatively high doses of perchlorates has been studied in humans with hyperthyroidism and animals, but data concerning long-term low-dose exposure are limited, as are data regarding the possible effects of perchlorate on the hematological system. The data base also lacks developmental and 2-generation reproductive studies. Reflecting confidence in the principal study and the data base, confidence in the RfD for potassium perchlorate and sodium perchlorate is low.

III. CANCER RISK ASSESSMENT FOR PERCHLORATES

A. THYROID FOLLICULAR CELL CARCINOGENESIS

All of the data pertinent to the possible carcinogenicity of the perchlorates is related to the effects of the perchlorate ion on the follicular cells of the thyroid gland. It has been demonstrated in animal and human studies and <u>in vitro</u> that perchlorate competitively inhibits the uptake of iodide by the thyroid (Stanbury and Wyngaarden, 1952; Wyngaarden et al., 1952 and 1953; Wolff and Maurey, 1962; Saito et al., 1983). These

studies were reviewed in Sections II. A and B. Before discussing specific studies related to carcinogenicity, it is useful to review what is known regarding the genesis of thyroid follicular cell tumors in animals and humans. A convincing body of information is available which suggests that long-term interference with normal thyroid-pituitary homeostasis can lead to thyroid follicular cell neoplasia. This phenomenon has been the subject of two extensive reviews (U.S. EPA, 1988; Hill et al., 1989), and will be summarized briefly here. (These two reviews had the same principal authors and are essentially interchangeable).

The normal control of thyroid hormone levels is maintained by a feedback mechanism (described above in Section II.) in which thyroid-stimulating hormone (TSH), secreted by the anterior pituitary, stimulates the thyroid follicular cells to begin synthesis of thyroid hormones. Circulating levels of thyroid hormones (T4 and T3) in turn inhibit the synthesis of TSH in the pituitary. Therefore, high plasma levels of thyroid hormones reduce the amount of TSH produced, while low plasma levels of thyroid hormones result in increased TSH production and release from the pituitary. If thyroid hormones are not produced in response to TSH, plasma levels of TSH remain high, resulting in an ongoing stimulation of the thyroid gland. This may occur under any conditions which induce hypothyroidism, such as iodine insufficiency, or via chemically-induced interference with thyroid hormone synthesis.

Numerous animal studies have shown that chronic stimulation of the thyroid by TSH leads to a predictable sequence of histological responses (reviewed in U.S. EPA, 1988). Initially, hypertrophy of the follicular epithelial cells is observed: the follicular cells increase in volume as colloid is resorbed from the follicular lumen, and the cells change from low cuboidal epithelia to a more columnar form. This phase is followed by a period of follicular cell hyperplasia, resulting in rapid increases in the size and weight of the thyroid. The increase in thyroid weight eventually reaches a plateau. When stimulation by TSH continues, the diffuse hyperplasia may progress to the formation of hyperplastic nodules, adenomas and finally to malignant tumors.

It is important to note that the histological progression described above is similar regardless of the cause of thyroid insufficiency. Hill et al. (1989) named six conditions which can lead to thyroid hyperplasia in animals and goiter in humans: 1) lack of dietary iodide; 2) blockage of iodide uptake into the thyroid; 3) interference with thyroid hormone synthesis (by inhibition of thyroid peroxidase); 4) suppression of thyroid activity by high concentrations of iodide; 5) enhanced metabolism of thyroid hormones and 6) damage to the thyroid gland (for example, by ionizing radiation, or by subtotal thyroidectomy in

animals). Progression from hyperplasia to neoplasia in animals requires ongoing stimulation by excess TSH. Removal of this stimulus, by administration of thyroid hormones, for example, may halt or even reverse the morphological progression described above. The progression from hyperplasia to neoplasia in humans is not well documented. The only factor which has shown a definitive association with thyroid cancer in humans is ionizing radiation. While epidemiologic data suggest that the risk of thyroid cancer is related to preexisting goiter and thyroid nodules, according to Hill et al. (1989), it appears that humans may be less sensitive than animals to the effects of long-term stimulation of the thyroid by TSH.

From the foregoing discussion it is apparent that thyroid cancer induced by interference with thyroid homeostasis is a threshold phenomenon. This conclusion is supported by evidence that many of the chemicals which induce (only) thyroid cancer in animals are only weakly or are not at all genotoxic (reviewed in U.S. EPA, 1988 and Hill et al., 1989).

B. REVIEW OF CARCINOGENICITY DATA

No human data are available to assess the carcinogenic potential of the perchlorates. While potassium perchlorate has been used therapeutically (for varying lengths of time) to treat hyperthyroidism since the 1950s, no studies have been designed to examine the question of carcinogenicity. It should be recognized that since the objective in treating this condition is to attain a euthyroid status, it is unlikely that excessive levels of TSH would be found in patients receiving long term treatment with potassium perchlorate.

The animal studies in which thyroid tumors were observed following potassium perchlorate administration have been discussed in Section II.B. However, a few additional comments are warranted here.

Kessler and Kruskemper (1966) administered potassium perchlorate to male Wistar rats at a level of 1% in the drinking water for up to 2 years. Histological examination of the thyroid at interim sacrifices revealed changes to the gland which are characteristic of chronic thyroid insufficiency: an initial hypertrophy with high epithelia and large nuclei by 40 days, a peak in thyroid weight at 120 days which then declined somewhat by 220 days, showing diffuse struma (or goiter) and degenerative changes. By 730 days, thyroid adenomas, described by the authors as "circumscribed", had developed in 4 of 11 rats. The thyroid weights in rats with tumors was very high compared to either the control animals or the other treated rats (88-221 mg, compared to means of 41.7 mg in 7 treated rats, and 26.6 mg in 6 control rats). Thus, it appears that extreme hyperplasia correlated with

tumor induction. While it is clear that tumors were observed, there were limitations in the reporting of the study. It was unclear whether there was any mortality among the dosed animals since the authors did not state the number of animals in the beginning of the study. The lack of difference in body weights between control and treated animals suggests that the dose was not overtly toxic. The authors stated that no tumors were observed in 20 control animals, but body weight data was provided for only 6 animals at 730 days. No information on drinking water consumption was provided, so the actual dose the animals received is unknown.

Gauss (1972) provided female NMRI mice (number not specified) a diet containing 1% potassium perchlorate for up to 160 days. The progressive histological changes to the thyroid, described in Section II. B., appeared characteristic of chronic thyroid deficiency. The authors described areas of adenomatic tissue and adenoma complexes in treated animals, but no malignancy. The authors also stated that the "structural deformations" of the thyroid were at least in part reversible following cessation of treatment. These data could be considered as suggestive, rather than definitive, evidence of carcinogenicity. Interpretation was limited by the lack of an English translation and by limitations in the reporting of the data.

Pajer and Kalisnik (1991) administered drinking water containing 0 or 1.2% sodium perchlorate to groups of 36 female BALB/c mice for up to 46 weeks. The daily dose was estimated at 2147 mg/kg-day. Twelve mice from each group received irradiation, leaving 24 mice from the control and perchlorate-treated groups for the assessment of effects of perchlorate on the thyroid. Thirty animals died during the treatment period. While no details were provided regarding these deaths, it appeared that only 6 of 24 animals treated with perchlorate alone survived, suggesting that the treatment was highly toxic. Histological changes in the thyroid glands of treated animals included hypertrophy, hyperplasia and a marked increase in the total volume of the gland (65 mm^3 in treated mice vs. 3 mm^3 in controls). Follicular cell carcinoma was reported in 5/6 perchlorate-treated mice, 14/14 in perchlorate-irradiated mice and 0/22 in control mice.

Hiasa et al. (1987) examined tumor promoting effects of potassium perchlorate (0 or 1000 ppm in the diet) in groups of 20 male Wistar rats given either a single i.p. injection of the carcinogen N-bis(2-hydroxypropyl)nitrosamine (DHPN) or no injection. The daily dose of potassium perchlorate was estimated as 80.7 mg/kg-day. After 20 weeks the thyroid glands were examined grossly and histologically. Thyroid weights were significantly higher in animals treated with perchlorate alone

relative to untreated controls. The perchlorate diet following DHPN led to significantly increased thyroid weight (compared to DHPN controls) and the development of both adenomas and carcinomas in 100% (20/20) of the animals. Most of the adenomas were classified as follicular in origin (218/246), 19 were papillary and 9 were solid. The carcinomas were described as solid in 23/31 cases, while 4 each were follicular cell and papillary carcinomas. Follicular cell hyperplasia was reported in 1/20 of the animals treated with perchlorate alone, but no tumors were observed. No tumors were observed in 20 untreated controls. Increased serum levels of TSH were measured in perchlorate-treated rats, as compared to rats receiving the basal diet. However, the levels were not as greatly elevated as those seen with the administration of other less potent tumor promoters (potassium iodide and propylthiouracil). Because of the short duration of the study, it cannot be assumed that rats receiving this dose level of potassium perchlorate for a longer period would not develop thyroid tumors.

C. WEIGHT-OF-EVIDENCE CLASSIFICATION AND QUANTITATIVE ESTIMATE

Although the studies described above used small numbers of animals and were lacking in quantitative information such as drinking water consumption, it is clear that thyroid tumors were induced in both rats and mice by long-term administration of high doses of perchlorates. The Pajer and Kalisnik (1991) study showed most perchlorate-treated animals with malignant tumors after only 46 weeks. Therefore, in spite of the limitations of the studies, the data warrant a classification of B2, probable human carcinogen.

No genotoxicity studies were found in the literature searches for potassium perchlorate. One study was identified which initially seemed to indicate that sodium perchlorate inhibited the growth of DNA polymerase-deficient bacteria (Rosenkranz, 1973). However, close examination of the paper suggests that the inclusion of perchlorate in one table is most likely a typographical error which should have been perborate. Attempts to contact the author for verification were unsuccessful.

The evidence regarding the mechanism of action of the perchlorates strongly suggests that the induction of thyroid cancer results from sustained disruption of the thyroid-pituitary axis due to inhibition of iodide uptake by the thyroid gland. Additional support for this hypothesis is provided by studies on the effect of iodine deficient diets in rats. Ohshima and Ward (1986) investigated the induction of thyroid tumors in groups of 30 male F344/NCr rats which had been administered a single injection of either N-nitrosomethylurea (NMU, 41.2 mg/kg) or citrate buffer. Rats of both treatment groups were then placed

on an iodine-deficient diet (IDD) or iodine-adequate diets (IAD; one lab diet and one commercial diet). The rats were sacrificed at 52 or 77 weeks, or when moribund. Nearly all NMU-treated rats developed thyroid tumors by 52 weeks. Follicular cell adenoma or carcinoma was observed in 100% of rats in the NMU/IDD group and in 67 and 82% of rats in the NMU/IAD groups. In the vehicle-treated/IDD rats, follicular cell adenomas were seen in 4/10 rats at 52 weeks and 12/20 rats at 77 weeks. Follicular cell carcinoma was seen in 2/20 IDD rats at 77 weeks. No thyroid follicular cell tumors were seen in either group of vehicle-treated/IAD rats. These data indicate that iodine deficiency alone is sufficient to produce thyroid tumors in rats.

The perchlorates present an unusual case with regard to derivation of a quantitative risk estimate for carcinogenicity. Because there is good support for the hypothesis that there is a threshold for the carcinogenic effect, a linear extrapolation to estimate low dose risk would be inappropriate. In addition, the studies in which tumors were observed are inadequate for the derivation of a quantitative estimate because of small numbers of animals, use of single dose levels, lack of consumption data and high mortality.

When sufficient information is available for carcinogens which act by threshold mechanisms, it may be appropriate to consider the RfD as a dose which does not pose a significant risk of cancer. The use of this approach is discussed in U.S. EPA (1988). For perchlorates, this would at first seem reasonable since the underlying mechanism of carcinogenicity is the same as that for systemic toxicity, that is, the inhibition of iodide transport into the thyroid. Two important limitations of the perchlorate database with respect to potential carcinogenicity preclude the use of such an approach. One is that no comprehensive cancer bioassays of the perchlorates have been carried out, in which anatomical sites other than the thyroid or the pituitary were examined. A second limitation is that while no genetic toxicity data were found, there is no indication that perchlorates have been adequately tested. If there were data available to show that the perchlorates were not genotoxic and induced no tumors at sites other than the thyroid, it would be reasonable to conclude that chronic exposure to levels below the RfD would not pose a significant risk of cancer in humans. However, the data are insufficient to support such a conclusion. Therefore, no quantitative estimate of carcinogenic risk can be derived for perchlorates at the present time.

IV. REFERENCES

Anonymous. 1969. Drug Treatment of Thyrotoxicosis. Br. Med. J. 2: 496-497.

Barzilai, D. and M. Sheinfeld. 1966. Fatal complications following use of potassium perchlorate in thyrotoxicosis. Israel J. Med. Sci. 2(4): 453-455.

Biswas, N., Y. Ahn, J.M. Goldman and J.M. Schwartz. 1991. Case report: Aplastic anemia associated with antithyroid drugs. Am. J. Med. Sci. 301(3): 190-199.

Brown-Grant, K. 1966. Failure of orally administered perchlorate to affect deciduoma formation or pregnancy in the rat. J. Reprod. Fert. 12: 353-357.

Brown-Grant, K. and M.R. Sherwood. 1971. Viability of the rat blastocyst following the oral administration of potassium perchlorate or potassium iodide to the mother. J. Reprod. Fert. 27: 265-267.

Burgi, H., M. Benguerel, J. Knopp, H. Kohler and H. Studer. 1974. Influence of perchlorate on the secretion of non-thyroxine iodine by the normal human thyroid gland. Europ. J. Clin. Invest. 4: 65-69.

Connell, J.M.C. 1981. Long-term use of potassium perchlorate. Postgrad Med. J. 57: 516-517.

Crooks, J. and E.J. Wayne. 1960. A comparison of potassium perchlorate, methylthiouracil, and carbimazole in the treatment of thyrotoxicosis. Lancet 1: 401-404.

DeGroot, L.J. and U. Buhler. 1971. Effect of perchlorate on iodine metabolism. Acta Endocrinol. 68: 696. (Cited in Burgi et al., 1974.)

Durand, M.J. 1938. Recherces sur l'elimination des perchlorates, sur leur repartition dans les organes et sur leur toxicite. Bull. Soc. Chim. Biol. 20: 428-435.

Everd, D.C. 1976. Endocrine and metabolic diseases; Treatment of thyroid disease: I. Br. Med. J. 1: 264-266.

Fawcett, J.W. and C.W.F. Clarke. 1961. Aplastic anaemia due to potassium perchlorate. Br. Med. J. 1: 1537.

Gauss, W. 1972. Das verhalten einiger physiologischer und histologischer kriterien der schilddrusenfunktion bei einmaliger oder langerer verabreichung von kaliumperchlorat an adulte mause. Z. Mikrosk-anat. Forsch. 85(4): 469-500.

Gjemdal, N. 1963. Fatal aplastic anaemia following use of potassium perchlorate in thyrotoxicosis. Acta Med. Scand. 174(2) 129-131.

Godley, A.F. and J.B. Stanbury. 1954. Preliminary experience in the treatment of hyperthyroidism with potassium perchlorate. J. Clin. Endocrinology 14: 70-78.

Goldman, S.J. and J.B. Stanbury. 1973. The metabolism of perchlorate in the rat. Endocrinology 92(5): 1536-1538.

Hiasa, Y., Y. Kitahori, Y. Kato et al. 1987. Potassium perchlorate, potassium iodide, and propylthiouracil: Promoting effect on the development of thyroid tumors in rats treated with N-bis(2-hydroxypropyl)-nitrosamine. Jpn. J. Cancer Res. 78: 1335-1340.

Hill, R.N., L.S. Erdreich, O.E. Paynter, P.A. Roberts, S.L. Rosenthal and C.F. Wilkinson. 1989. Thyroid follicular cell carcinogenesis. Fund. Appl. Toxicol. 12: 629-697.

Hobson, Q.J.G. 1961. Aplastic anaemia due to treatment with potassium perchlorate. Br. Med. J. 1: 1368-1369.

ICF Technology Inc. (Undated). On the Toxicity of Perchlorates. ICF Technology Inc. Oakland, CA.

Johnson, R.S. and W.G. Moore. 1961. Fatal aplastic anaemia after treatment of thyrotoxicosis with potassium perchlorate. Br. Med. J. 1: 1369-1371.

Kessler, F.J. and H.L. Kruskemper. 1966. Experimentell schilddrusentumoren durch mehrjahrige zufuhr von kaliumperchlorat. Klin. Wochenschr 44: 1154-1156.

Kotzaurek, R. 1965. Nil nocere!: Akute leberatrophie nach perchlorat-therapie. Munch. Med. Wochenschr. 42: 2067-2070.

Krevans, J.R., S.P. Asper, Jr. and W.F. Rienhoff. 1962. Fatal aplastic anemia following use of potassium perchlorate in thyrotoxicosis. J. Amer. Med. Assoc. 181(2): 162-164.

Mannisto, P.T., T. Ranta and J. Leppaluoto. 1979. Effects of methylmercaptoimidazole (MMI), propylthiouracil (PTU), potassium perchlorate ($KClO_4$) and potassium iodide (KI) on the serum

concentrations of thyrotrophin (TSH) and thyroid hormones in the rat. Acta. Endocrinology 91: 271-281.

Morgans, M.E. and W.R. Trotter. 1960. Potassium perchlorate in thyrotoxicosis. Br. Med. J. 2: 1086-1087.

NIOSH (National Institute for Occupational Safety and Health). 1992. RTECS (Registry of Toxic Effects of Chemical Substances). U.S. DHHS, PHS, CDC, Cincinnati, OH. August, 1992.

Ohshima, M. and J.M. Ward. 1986. Dietary iodine deficiency as a tumor promoter and carcinogen in male F344/NCr rats. Cancer Res. 46: 877-883.

Pajer, Z. and M. Kalisnik. 1991. The effect of sodium perchlorate and ionizing irradiation on the thyroid parenchymal and pituitary thyrotropic cells. Oncology 48: 317-320.

Postel, S. 1957. Placental transfer of perchlorate and triiodothyronine in the guinea pig. Endocrinology 60: 53-66.

Rockette, H.E. and V.C. Arena. 1983. Mortality patterns of workers in the Niagara plant. Submitted by Occidental Chemical Corp to U.S. EPA under TSCA. Microfiche #OTS0537001.

Rosenkranz, H.S. 1973. Sodium hypochlorite and sodium perborate: preferential inhibitors of DNA polymerase-deficient bacteria. Mutation Res. 21: 171-174.

Saito, K., K. Yamamoto, T. Takai and S. Yoshida. 1983. Inhibition of iodide accumulation by perchlorate and thiocyanate in a model of the thyroid iodide transport system. Acta Endocrinology 104: 456-461.

Southwell, N. and K. Randall. 1960. Potassium perchlorate in thyrotoxicosis. Lancet 1: 653-654.

Stanbury, J.B. and J.B. Wyngaarden. 1952. Effect of perchlorate on the human thyroid gland. Metabolism. 1: 533-539.

Sunar, O. 1963. Case report-agranulocytosis associated with potassium perchlorate treatment. J. Laryng. 77: 353-354.

U.S. EPA. 1987. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Prepared by Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. ECAO-CIN-554.

U.S. EPA. 1988. Thyroid Follicular Cell Carcinogenesis: Mechanistic and Science Policy Considerations. Office of Research and Development, Washington, DC. NTIS No. PB88-230750.

U.S. EPA. 1991. Office of Health and Environmental Assessment Chemical Assessments and Related Activities. Office of Health and Environmental Assessment, Washington, DC. April, 1991. OHEA-I-127.

U.S. EPA. 1992a. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1992b. Health Effects Assessment Summary Tables. Annual FY-1991. Office of Research and Development, Office of Emergency and Remedial Response, Washington, DC. NTIS PB91-921100.

U.S. EPA. 1992c. Monthly Status Report of RfD/RfC Work Group (As of 11/01/92). Office of Research and Development. Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1992d. Drinking Water Regulations and Health Advisories. Office of Drinking Water, Washington, DC. April, 1992.

Weber, A. and J. Wolf. 1969. Nephrotisches syndrom unter thyreostatischer behandlung mit natriumperchlorat. Uas der Med. Univ.-Klinik Marburg. 44: 2274-2275.

Wolff, J. and J.R. Maurey. 1963. Thyroidal iodide transport: IV. the role of ion size. Biochim. Biophys. Acta. 69: 48-58.

Wyngaarden, J.B., B.M. Wright and P. Ways. 1952. The effect of certain anions upon the accumulation and retention of iodide by the thyroid gland. Endocrinology 50: 537-549.

Wyngaarden, J.B., J.B. Stanbury and B. Rapp. 1953. The effects of iodide, perchlorate, thiocyanate, and nitrate administration upon the iodide concentrating mechanism of the rat thyroid. Endocrinology 52: 568-574.